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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/105,117	06/17/1998	MARINA VRLIJC	FJ-122	5178

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EXAMINER	
MITRA, RITA	

ART UNIT	PAPER NUMBER
1653	39

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Please find below and/or attached an Office communication concerning this application or proceeding.

File Copy

Office Action Summary	Application No. 09/105,117	Applicant(s) VRLIJC ET AL.	
	Examiner Rita Mitra	Art Unit 1653	

-- The MAILING DATE of this communication appears on the cov r sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 February 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20 and 43-48* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-20 and 43-48* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Status of the Claims

Applicants' amendment and response to office action dated October 22, 2001 in paper #35 filed on February 19, 2002 is acknowledged. Claims 1, 3, 4 and 13 have been amended and entered. It should be noted that the response at page 2 reads as "... amend the present application..." However, to continue the prosecution without interruption it was interpreted as "...amend the claims...". It is incumbent upon the Applicants to make an appropriate correction. Therefore, claims 1-20 and 43-48 are currently pending to which the following grounds for rejection are or remain applicable.

Rejection under 35 U.S.C. 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1 and dependent claims 2-20 stand/are rejected under **35 U.S.C. 112, first paragraph**, because the specification, while being enabling for a process for microbacterial production of amino acids by providing a microbial organism having a certain export carrier activity and a certain export gene expression, wherein the export gene amino acid sequence is set forth in SEQ ID NO: (A) 2 and a regulatory protein sequence is set forth in SEQ ID NO: (B) 3; does not reasonably provide enablement for a process using allele variants of export carrier protein and regulatory proteins of SEQ ID NO: (A)2 and SEQ ID NO: (B)3 respectively. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claim 1and the dependent claims 2-20 thereto are directed to a process for the microbial production of amino acids using a gene construct, having an export gene that encodes an amino acid sequence of SEQ ID NO: (A) 2, wherein the regulatory gene of the construct encodes an amino acid sequence as set forth in SEQ ID NO: (B) 3 and the allelic variants thereof. The specification, however, only discloses cursory conclusions (see page 6), without data to support the findings, which state that in general a functional derivative that can be obtained by mutation but it does not provide a definition of an allelic variant. There are no indicia that the present application enables the full scope in view of the amino acid sequences corresponding to an export gene and a regulatory gene products as set forth in SEQ ID NO: (A) 2 and SEQ ID NO: (B) 3 or an allelic variant thereof as discussed in the following stated rejection. The present application provides no indicia and no teaching/guidance as to how the full scope of the claims is encompassed.

In this regard, the application disclosure and claims have been compared per the factors indicated in the decision *In re Wands*, 8 USPQ2d 1400 (Fed. Cir., 1988) as to undue experimentation. The factors include: 1) the nature of the invention; 2) the breadth of the claims 3) the amount of direction or guidance presented; 4) the presence or absence of working examples; 5) the quantity of experimentation necessary; 5); 6) the predictability or unpredictability of the art; 7) the state of the prior art; and, 8) the relative skill of those skilled in the art;

Each factor is addressed below on the basis of comparison of the disclosure, the claims and the state of the prior art in the assessment of undue experimentation.

1) the nature of the invention:

The nature of the invention is defined by the claims, which include a process for the microbacterial production of amino acids by providing a microbial organism using a gene construct, having an export gene that encodes an amino acid sequence of SEQ ID NO: (A) 2, wherein the regulatory gene of the construct encodes an amino acid sequence as set forth in SEQ

ID NO: (B) 3 and the allelic variants thereof. However the specification does not provide the information on the structure and function of the claimed allele variants.

2) the breadth of the claims:

The breadth of the claims is broad and encompasses an unspecified number of variants regarding the export gene protein of SEQ ID NO: (A) 2 and a regulatory protein of SEQ ID NO: (B) 3 as biological active fragments, which are not specifically described or demonstrated in the specification. The specification describes at page 6 as "allelic variations or, respectively, equally effective DNA sequences comprise particularly functional derivatives which can be obtained by deletions, insertion or substitution of nucleotides of corresponding sequences..." However the specification at page 6, lines 7-19 describes a functional derivative that can be obtained by mutation but it does not provide a definition of an allelic variant. It was stated in the previous office action that an allele is "one of two or more alternative forms of a gene, each possessing a unique nucleotide sequence; different alleles of a given gene are usually recognized, however, by the phenotypes rather than by comparison of their nucleotide sequences." The specification does not describe what might be considered an allele of the DNA of claims 8 and 16 or provide any examples of the same. It does not appear that allelic variants have been isolated or identified. There are no examples of allelic sequences of the claimed DNA to which one could compare undisclosed DNA to determine if they are also alleles.

The comments at pages 3-4 of the response filed on Feb 19, 2002 is noted but are found unpersuasive. Applicants assert at page 3 that a change of the nucleotide sequence may be noticeable phenotypically in that the protein coded by the allele, the gene variation has changed the specific activity (for example, increased or reduced). However, since diploid organism carry two copies of each gene, they may carry identical alleles or carry different alleles. In a recessive mutation both the alleles must be mutant in order to show the mutant phenotype, while in dominant mutation are observed in a heterozygous individual carrying one mutant and one normal allele. It is known that the recessive mutations may remove part of or all the gene from the chromosome, disrupt expression of the gene, or alter the structure of the encoded protein, thereby altering its function, whereas dominant mutation often, but not always, result in a gain of

function. For example, dominant mutation, may increase activity of a given gene product or confer a new activity on the gene product (see Lodish et al. "Molecular Cell Biology", Fourth edition, Chapter 8, page 255, column 2). The specification fails to provide any description of the claimed alleles with the same function as the wild type gene. Therefore, as the function of the allelic variants depends on the type of the mutation (recessive or dominant) and the specification fails to describe adequately the structure and function of those allelic variants, one skilled in the art would not recognize a specific utility for the allelic variants and would not know how to use them. Thus, for the reasons set forth above, undue experimentation is required to make and use the claimed allele variants.

As for factors 3-5:
3) the amount of direction or guidance presented;
4) the presence or absence of working examples; and
5) the quantity of experimentation necessary:

The specification at page 6 provides a generic description for obtaining allelic variants by deletion, insertion and/or substitution of nucleotides of corresponding sequences, wherein however the regulator protein activity or function is retained or even increased. Furthermore, the specification describes and demonstrates the production and increased accumulation of L-lysine by export gene (LysE) and regulator gene (LysG) in Example f at page 3, however no description or Examples are provided for the enablement of claimed variants. The experimentation involved to enable the invention may constitute routine experimentation, however, because of the limited information in the specification it would require undue and excessive experimentation. No specific description is provided about the position of the corresponding sequence of SEQ ID NO: (A)2 and SEQ ID NO: (B)3 where amino acid substitution is suggested neither any activity of those variants have been demonstrated. Without more guidance from the specification it would require an undue and excessive experimentation for a person having skill in the art to be able to make and use the claimed analogs.

6) the predictability or unpredictability of the art:

The invention is highly unpredictable for the reasons set forth for factors 1-5.

As for factors 7 and 8:

7) the state of the prior art

8) the relative skill of those skilled in the art:

The prior art has shown that the flux of L-lysine biosynthesis in wild-type *Corynebacterium glutamicum* is increased by L-methionine addition (see Vrljic et al. J. of Bacteriology, vol 177 (4), July 1995), however, the general knowledge and level of the skill in the art do not supplement the omitted description, the specification needs to provide specific guidance on the structure and function for allelic variants.

In consideration of each of factors 1-8, it is apparent that there is undue experimentation because in summary, the scope of the claim is broad, the working example does not demonstrate the claimed variants, the guidance/the teaching in the specification is limited, and the outcome is unpredictable for the various modified forms, it is necessary to have additional guidance and to carry out further experimentation to assess the property of the variants. Therefore, due to large quantity of experimentation necessary to determine an activity or property of the disclosed process using export gene and the variants thereof, such that it can be determined how to use the claimed process, the lack of direction/guidance presented in the specification regarding same, the absence of working examples directed to same, the complex nature of the invention, the specification fails to teach the skilled artisan how to make and use the claimed invention.

Rejection under 35 U.S.C. 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

"The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention."

Claims 1-20, 44 and 45 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is indefinite because of extraneous periods (see "SEQ ID NO. (A)2"), which should be "SEQ ID NO:". It is also unclear where in the sequence listing that sequence (A)2 is located. Reference to the Table in this and other claims is inappropriate reference to the Table, which should be inserted into the claim else not referred to in the claim. The sequence listing has no "(A)1" or "(A)2". SEQ ID NO: should be followed with a numerical value only, not an alpha-numeric value.

Claim 1 is also indefinite, which recites "or a DNA sequence with essentially the same effects...". What is/are essentially the same effects?

Claims 2, 3, 4 are indefinite because refer to increased endogenous export activity. Compared to what is the activity increased?

Claims 4 and 5 are indefinite as to increased number of copies because when the number of copies is increased, but where the claim does not recite expression from the additional copies, it is not apparent that expression is increased.

Claim 6 is indefinite since the claim recites increased expression but from a low copy number vector. This is indefinite since it is not apparent how increase is affected by low copy number as opposed to high copy number.

Claim 7 is unclear as to whether or not "regulatory sequences assigned to the export gene" is or is not meant to have operative linkage.

Claim 8 is unclear because how or where there is definition of a regulatory sequence includes a segment that is a coding domain.

Claims 8, 9, 16, 18 and 19 are indefinite because reference to the Table is inappropriate reference to the Table, which should be inserted into the claim else not referred to in the claim.

Claims 10-20 are improperly multiply dependent from a previous (claims 7, 10, 12, 13, 14, 15, 17, 18, 19) multiply dependent claim.

Claims 43-48 are indefinite because they lack essential steps as claimed in the process for the microbacterial production of amino acids. The omitted steps are: the method of construction of a gene construct, insertion of the construct into a suitable vehicle and transformation of a suitable host cell, culturing the transformed cells and recovering the amino acids from the culture, and a step whereby the desired outcome can be determined.

Claim 44 is indefinite as to the "mutants." The term "mutated export gene" renders the claim indefinite. It is not clear what kind of mutants they are, e.g. what kind of a modification is made on the export gene sequence and whether those mutants are retaining the activity of the intact export gene. Claim 45 is included in the rejection because it is dependent on rejected claim and does not correct the deficiency of the claim from which they depend.

Claims 43-48 provides for the use of export gene, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 43-48 are rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

Conclusion

No claims are allowed.

Inquiries

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Rita Mitra whose telephone number is (703) 605-1211. The Examiner can normally be reached from 9:30 a.m. to 6:30 p.m. on weekdays. If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Dr. Christopher Low, can be reached at (703) 308-2923. Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The Fax Center number is (703) 308-4242. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

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Rita Mitra, Ph.D.
May 18, 2002